REMARKS

Reconsideration of the application and entry of the foregoing amendments are requested.

Claims 10, 25, and 34 have been cancelled, and claims 42 to 45 have been added. Claims 1, 7 to 9, 11 to 17, 20, 27, 31 to 33, and 35 to 45 are pending in the application. A total of 27 claims are pending, with two claims being independent. Applicants previously paid for 28 claims so no additional claims fee is due.

Claims 1, 7, 20, and 31 have been amended to specify that the mutations are "defined" mutations. Support for these amendments is in original claim 10 and page 6, lines 30 and 31, of the specification. Claims 42 to 45 recite preferred types of mutation in the *surA* gene, namely deletion and insertion mutations. Support for these claims is, for example, at page 6, lines 24 to 28, of the specification.

Applicants note that the Examiner has withdrawn all previous rejections but has made new rejections under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103. Applicants will address each of the new rejections below in the order in which they are set forth in the Official Action.

Response to rejection of new matter under 35 U.S.C. § 112, first paragraph

Applicants request withdrawal of this rejection in view of the following submissions.

The Examiner stated that Applicants did not point to support in the specification for a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in the *surA* gene and carrier. Applicants will therefore now point to such support: support is in, for example, original claims 1 and 6; page 1, lines 9 to 13; page 2, lines 15 to 18; page 3, lines 16 to 18 and page 6, line 24.

The Examiner argued that there is "no support for a composition that distinguishes a composition comprising pathogenic or non-pathogenic bacteria." However, Applicants respectfully submit that it would be abundantly clear to a skilled reader that the whole point of the invention is to take a pathogenic bacterium and attenuate it so as to make it non-pathogenic but still invoke an immune response. In light of the whole purpose of the work described in the application, it would make no sense to start from a non-pathogenic bacterium because such a bacterium is not capable of being attenuated (i.e., reduced in pathogenicity). The requirement to start from a pathogenic bacterium is made expressly clear in the specification in, for example, the first sentence of the Summary of the Invention at page 2, lines 15 to 18, where it is stated that:

> The original aim of the work that led to the invention was the identification of novel genes that are involved in the virulence pathways of pathogenic bacteria, the identification and deletion of which may render the bacteria avirulent and suitable for use as vaccines.

Similarly, the first paragraph of the Background to the Invention at page 1, lines 9 to 13, states that:

> The principle behind vaccination is to induce an immune response in the host thus providing protection against subsequent challenge with a pathogen. This may be achieved by inoculation with a live attenuated strain of the pathogen (i.e. a strain having reduced virulence such that it does not cause the disease caused by the virulent pathogen).

Response to rejection of lack of written description under 35 U.S.C. § 112, first paragraph

Applicants have now amended claims 1, 7, 20, and 31 to specify that the mutations are "defined" mutations. Applicants request withdrawal of the rejection in light of the amendment and the following submissions.

In making the rejection, Applicants respectfully submit that the Examiner has focussed on what is described in the Examples of the application and has not addressed the fact that the preceding part of the specification contains a very detailed general description of the nature of the mutations that may be made. See the passage at page 6, line 10, to page 7, line 23, which is reproduced here for the convenience of the Examiner:

> **The nature of the mutation**
>
> The mutations introduced into the bacterial vaccine generally knock-out the function of the gene completely. This may be achieved either by abolishing synthesis [of] any polypeptide at all from the gene or by making a mutation that results in synthesis of non-functional polypeptide. In order to abolish synthesis of any polypeptide, either the entire gene or its 5'-end may be deleted. A deletion or insertion within the coding sequence of a gene may be used to create a gene that synthesises only non-functional polypeptide (e.g. polypeptide that contains only the N-terminal sequence of the wild-type protein). In the case of mutations in genes encoding proteins which promote the folding of extracytoplamic proteins, the mutation generally abolishes the ability of the protein to promote such protein folding.
>
> The mutations are non-reverting mutations. These are mutations that show essentially no reversion back to the wild-type when the bacterium is used as a vaccine. Such mutations include insertions and deletions. Insertions and deletions are preferably large, typically at least 10 nucleotides in length, for example from 10 to 600 nucleotides.

> The bacterium used in the vaccine preferably contains only defined mutations, i.e. mutations which are characterised. It is clearly undesirable to use a bacterium which has uncharacterised mutations in its genome as a vaccine because there would be a risk that the uncharacterised mutations may confer properties on the bacterium that cause undesirable side-effects.
>
> The attenuating mutations may be constructed by methods well known to those skilled in the art (see ref 31). One means for introducing non-reverting mutations into extracytoplamic proteins is to use transposon Tn*phoA*. This can be introduced into bacteria to generate enzymatically active protein fusions of alkaline phosphatase to extracytoplasmic proteins. The Tn*phoA* transposon carries a gene encoding kanamycin resistance. Transductants are selected that are kanamycin resistant by growing colonies on an appropriate selection medium.
>
> Alternative methods include cloning the DNA sequence of the wild-type gene into a vector, e.g. a plasmid or cosmid, and inserting a selectable marker into the cloned DNA sequence or deleting a part of the DNA sequence, resulting in its inactivation. A deletion may be introduced by, for example, cutting the DNA sequence using restriction enzymes that cut at two points in the coding sequence and ligating together the two ends in the remaining sequence. A plasmid carrying the inactivated DNA sequence can be transformed into the bacterium by known techniques. It is then possible by suitable selection to identify a mutant wherein the inactivated DNA sequence has recombined into the chromosome of the bacterium and the wild-type DNA sequence has been rendered non-functional in a process known as homologous recombination.

So, the specification does not merely describe the particular mutation of the Examples but also describes in detail other mutations that may be used to achieve the same effect. The specification makes clear that what is important is that the *surA* gene is disrupted, not the precise nature of the mutation used to effect the disruption. The exact nature of the mutation is not important and essentially any type of mutation in the *surA* gene, for example deletion and insertion mutations, could be used.

The rejection is not consistent with the established practice of the PTO. The PTO is in the practice of granting patents for inventions similar to the present invention which define the mutation in terms similar to the present claims. See, for example, U.S. Patent No. 5,527,529 (Dougan et al.) cited by the Examiner in item 5 of the May 7, 2003 Office Action and U.S. Patent No. 5,804,194 (Dougan et al., copy enclosed). These two patents concern inventions similar to the present application, except that according to the patents the mutation is in the *ompR* gene or the *htrA* gene, respectively, whereas according to the present application the mutation is in the *surA* gene. Claim 1 of U.S. Patent No. 5,527,529 defines the mutation using the language "a non-reverting mutation in the ompR gene", and U.S. Patent No. 5,804,194 defines the mutation using the language "a non-reverting mutation in the htrA gene". This language is very similar to the language used in the claims of the present application. Thus, the PTO has previously approved definitions of mutations in claims that are essentially the same as the definition in the present claims.

Response to rejection under 35 U.S.C. § 103

Applicants respectfully request withdrawal of this rejection in light of the following submissions.

The Examiner argued that "it would have been prima facie obvious at the time of applicants' invention to modify the pathogenic bacteria comprising a mutation in the surA gene as taught in Lazar et al., to further include mutations in one or more outer membrane regulation genes as taught by Dougan et al. . . . ."

Applicants submit that a skilled person would have had no motivation whatsoever to modify the bacteria comprising a mutation in the *surA* gene, as described in Lazar et al., in the manner suggested by the Examiner. Lazar et al. has nothing whatsoever to do with attenuating pathogenic bacteria in order to

produce compositions which invoke an immune response against the bacteria, but rather describes experiments to investigate the biochemical function that *surA* plays in the cell. Indeed, the bacteria used according to Lazar et al. are apparently non-pathogenic, laboratory strains of *E. coli*. There would be no motivation to add attenuating mutations such as those disclosed in Dougan et al. to the *E. coli* described in Lazar et al. because the *E. coli* are already fully attenuated (i.e., non-pathogenic). There would be no point in introducing attenuating mutations into a bacterial cell that is already non-pathogenic.

The Examiner is reminded that, in making a rejection under 35 U.S.C. § 103, it is only permissible to combine references where it would have been obvious to a skilled person at the time of the invention to make the combination. See e.g. M.P.E.P. § 2143.01, third paragraph, where it is stated that "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly of implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." There is no obvious reason why a skilled person would have combined Dougan et al. with Lazar et al. Dougan et al. is a relatively obscure U.S. patent and Lazar et al. is a relatively obscure publication in a scientific journal. The two references are in different fields; Dougan et al. is in the field of producing attenuated bacterial vaccines, whereas Lazar et al. has nothing whatsoever to do with vaccines. Thus, there is no reason why a skilled person who had read Lazar et al. would simultaneously have held Dougan et al. or any other reference relating to vaccines in the forefront of his/her mind.

Furthermore, the Examiner appears to have overlooked the fact that the claims require that the pathogenic bacterium is attenuated by the non-reversing mutation in the *surA* gene. Thus, the claims require that it is the mutation in the *surA* gene that is responsible for the attenuation. The claims do not cover

introducing a *surA* mutation into a non-pathogenic bacterium because such a bacterium is already attenuated and cannot be attenuated by a mutation in the *surA* gene. Therefore, the claims do not encompass introducing *surA* mutations into non-pathogenic, laboratory strains of bacterium as taught in Lazar et al. Thus, even if it was obvious for a skilled person to add a mutation as taught in Dougan et al. to the bacteria taught in Lazar et al. (and this is denied), the resulting bacteria would not fall within the scope of the bacteria recited in the claims.

It is respectfully submitted that the application is in condition for allowance, and a notice to that effect is requested.

Enclosed is a Form PTO-1449 listing three documents that were cited by the Examiner in the August 23, 2002 Office Action, but not formally made of record on a Form PTO-892 or PTO-1449. The attached Form PTO-1449 also lists U.S. Patent No. 5,804,194 (copy enclosed), which is discussed above.

If any additional fees are due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 16-2312. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

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